separable from the problems of air, land and water pollution, from the balance of human population with limited food, energy and other essential resources—and that these in turn are inseparable from the continuum of death, sickness, health and well-being which is the business of medicine. The enormity of this force, which focuses directly on what is actually involved in human health, and how it will shape the future of medicine, can only be imagined at this time.

These are some of the reasons why the public emphasis on health and the public expectations from medicine and health care seem here to stay, for the present and foreseeable future. The power of these forces is such that it would be folly to ignore them. It would seem that it is now time for the medical profession to take a new, long and hard look at what is actually involved in health, at what it takes to maintain human health and at how disturbances in human health lead to illness, injury and emotional disorder—as well as the reverse, which has been the traditional approach. If medicine is to continue to serve humanity as it has in the past, it must henceforth make health as much its business as sickness has been. The implications of this for medical education and for the role of medicine in society are considerable but the challenge should be met.

—MSMW

Pathogenesis of Systemic Lupus Erythematosus

THE DISCOVERY of the lupus erythematosus cell phenomenon over twenty-five years ago marked the start of the modern era of research into the pathogenesis of systemic lupus erythematosus (SLE). This initial clinical observation led to the finding of anti-nuclear factor and antibodies to deoxyribonucleic acid (DNA) in the sera of lupus patients. Further studies on renal eluates of lupus patients established the importance of DNA containing immune complexes in the causation of lupus glomerulonephritis, the major cause of death in this disease. As discussed in the paper by Bardana and Pirofsky elsewhere in the JOURNAL, the presence of antibodies to DNA and reduced serum complement have become routine correlates of active systemic lupus erythematosus, distinguishing this entity from other lupus variants.[1]

Although the consequences of antibodies to DNA are clear, the cause of this antibody formation is uncertain. Antibodies to single-stranded DNA occur in drug-induced lupus and other related disorders, and lack the specificity for systemic lupus erythematosus associated with antibodies to double-stranded DNA. Moreover, antibodies to single-stranded DNA can be induced by immunization of experimental animals with DNA complexed to protein and emulsified in Freund's adjuvant. Antibodies to double-stranded DNA cannot be provoked by experimental immunization, and occur almost exclusively in systemic lupus erythematosus and in New Zealand Black (NZB) mice, an animal model for SLE.[2,3]

It is not known whether viral or host DNA is the immunogen for anti-DNA antibodies. As discussed by Bardana and Pirofsky, several lines of evidence favor a role for virus in the pathogenesis of lupus. The presence of antibodies to viral surface antigens, to double-stranded ribonucleic acid (RNA) and to DNA:RNA hybrids is indirect evidence that immunization to viral antigens may be occurring in this disease. Antibodies to double-stranded RNA have a specificity for SLE intermediate between single and double-stranded DNA. They are seen in almost 50 percent of patients with discoid lupus erythematosus and in 70 percent of patients with the systemic disease. They are not necessarily associated with lupus nephritis, and not generally present in the renal immune complex deposits.

An additional antibody activity is also intimately associated with the pathogenesis of systemic lupus erythematosus. Lymphocytotoxic antibodies with specificity for thymic-derived lymphocytes occur in many SLE patients and in New Zealand Black mice. Such antibodies are capable of killing T lymphocytes in the presence of complement and of coating peripheral blood T cells so as to interfere with certain functional activities (such as response in an allogeneic mixed lymphocyte reaction) or with HL-A typing. These antibodies have specificity for T cell surface antigens and can be released from the lymphocyte cell surface in the form of specific antigen-antibody complexes. Such complexes may themselves attach and block other lymphocytes, or may contribute to immune complex deposition leading to vasculitis and nephritis.

A better understanding of the pathogenesis of

SLE has come from detailed studies of the immunologic status of NZB mice at various stages of their disease. These mice are genetically predisposed to the formation of LE cells, antinuclear factor, antinucleic acid antibodies, immune complex nephritis and autoimmune hemolytic anemia.

The overall immune status in SLE and in NZB mice can generally be summarized as an imbalance in which T cell activity is depressed and B cell activity is enhanced.[4] Delayed hypersensitivity responses may be impaired, in part due to the action of lymphocytotoxic antibodies. Antibody formation is both qualitatively and quantitatively excessive, with unusual (that is, autoantibody) and higher titered antibody responses occurring.

Autoantibody formation is normally prevented through the action of T regulatory lymphocytes called "suppressor T cells." Although the mechanism or mechanisms of suppression are unknown, such suppressor T cells probably play a very important role in immunologic tolerance and self/non-self discrimination. A deficiency of T supressor cells has been demonstrated in NZB mice preceding the development of autoimmunity.[5] This deficiency is related to a decrease in concentration of circulating thymic hormone.[6] Administration of thymic hormone to NZB mice can prevent this loss of T suppressor cells and delay the onset of autoimmunity.[5] A reversible loss of T suppressor cells could also explain the drug-induced lupus syndrome seen with procainamide.

As NZB mice age and clinical autoimmune disease becomes apparent, there is a marked loss of various T cell effector functions (for example, response to phytomitogens, ability to induce graft-versus-host disease and ability to reject malignant tumors). Such mice are immunologically impaired and susceptible to infectious agents and to oncogenic viruses. Lymphomas and monoclonal macroglobulinemia are common at this stage.[7-9] Since NZB mice harbor murine leukemia viruses, these lymphoid malignancies may be the final expression of impaired immune surveillance and defective immunologic suppression of viral induced malignancy.

Dubois[1] has emphasized the recent increased death rate from infection and malignancy as deaths from uremia and central nervous system complications have declined in SLE. These clinical observations parallel the experience with NZB mice. Furthermore, malignancy may be potentiated in autoimmune diseases, in renal transplant recipient patients and in NZB mice by the administration of immunosuppressive drugs. Because of this as well as other serious complications, immunosuppressive drugs should be used with discretion in patients with SLE and other autoimmune diseases.

The five-year survival rate in SLE has improved greatly and approaches 80 percent. As we gain understanding of the multifactorial cause of SLE, more rational forms of treatment based on pathophysiologic concepts should evolve. Such concepts may have important implications for oncology and aging as well as for the field of autoimmunity.

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Health Counseling

PRACTICING PHYSICIANS know that large proportions of their patients do not follow their instructions or advice, and public health officials have discovered that much of the public pays little attention to their warnings, dire as these may be. These instructions, warnings and advice all are given with the best of motivation. They attempt to tell the patient or the public what is good for their health. Unfortunately not everyone welcomes or accepts these well-intentioned efforts to tell them what they should do, and compliance—to use a term which is creeping into health care jargon—is considerably less than what is deemed desirable by those who give these authoritative instructions, advice or warnings.

These problems of health counseling have been given less attention than they deserve. It could